

Diagnosis and management of drug hypersensitivity reactions

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The present article addresses the advances in the diagnosis and management of drug hypersensitivity reactions that were discussed in the 4th Drug Hypersensitivity Meeting held in Rome in April 2010. Such reactions can be classified as immediate or nonimmediate according to the time interval between the last drug administration and onset. Immediate reactions occur within 1 hour, and nonimmediate reactions occur after more than 1 hour. Clinical and immunologic studies suggest that type-I (IgE-mediated) and type-IV (T cell-mediated) pathogenic mechanisms are involved in most immediate and nonimmediate reactions, respectively. In diagnosis prick, patch, and intradermal tests are the most readily available tools. Determination of specific IgE levels is still the most common *in vitro* method for diagnosing immediate reactions. New diagnostic tools, such as the basophil activation test, the lymphocyte activation test, and enzyme-linked immunosorbent assays for analysis of the frequency of antigen-specific, cytokine-producing cells, have been developed for evaluating either immediate or nonimmediate reactions. The sensitivity of allergologic tests is not 100%; therefore in selected cases provocation tests are necessary. In the diagnosis of nonallergic hypersensitivity reactions to nonsteroidal anti-inflammatory drugs, the provocation test with the suspected drug still represents the "gold standard." However, there was no consensus regarding the use of this test in subjects with histories of hypersensitivity reactions to 1 (single reactors) or more (multiple reactors) nonsteroidal anti-inflammatory drugs. With regard to management, desensitization allows patients to be treated with irreplaceable chemotherapy agents, such as taxanes, platinum salts, and mAbs, to which they have presented hypersensitivity reactions. Desensitization also permits the use of aspirin in aspirin-sensitive patients undergoing revascularization and in subjects with aspirin-exacerbated respiratory disease. (J Allergy Clin Immunol 2011;127:S67-73.)

Key words: Anticonvulsants, β -lactams, desensitization, diagnosis, drugs, hypersensitivity, nonsteroidal anti-inflammatory drugs

Abbreviations used

AERD:	Aspirin-exacerbated respiratory disease
AGEP:	Acute generalized exanthematous pustulosis
BAT:	Basophil activation test
DHM4:	4th Drug Hypersensitivity Meeting
DPT:	Drug provocation test
DRESS:	Drug reaction (or rash) with eosinophilia and systemic symptoms
ELISPOT:	Enzyme-linked immunosorbent spot
KLH:	Keyhole limpet hemocyanin
LAT:	Lymphocyte activation test
LTT:	Lymphocyte transformation test
NSAID:	Nonsteroidal anti-inflammatory drug
SJS:	Stevens-Johnson syndrome
TEN:	Toxic epidermal necrolysis

The revised nomenclature for allergy distinguishes between allergic and nonallergic hypersensitivity reactions to drugs and classifies the former as IgE-mediated or non-IgE-mediated.¹

In the 4th Drug Hypersensitivity Meeting (DHM4) there was a consensus concerning the importance of distinguishing between immediate and nonimmediate reactions for establishing the diagnosis and management of drug hypersensitivity reactions. Immediate reactions occur within the first hour after the last drug administration and are manifested clinically by urticaria, angioedema, rhinitis, bronchospasm, and anaphylactic shock. Nonimmediate reactions occur more than 1 hour after the last drug administration. The main nonimmediate reactions are maculopapular eruptions and delayed-appearing urticarial exanthema. Immediate allergic reactions are thought to be IgE-mediated and have been extensively studied, whereas the mechanisms involved in nonimmediate reactions seem to be heterogeneous.² However, clinical and laboratory studies indicate that a T cell-mediated pathogenic mechanism is often involved in maculopapular rashes. This mechanism has also been demonstrated in other nonimmediate reactions, such as urticarial manifestations, angioedematous manifestations, or both; toxic epidermal necrolysis (TEN); bullous exanthems; drug reaction with eosinophilia and systemic symptoms (DRESS); and acute generalized exanthematous pustulosis (AGEP).

In nonallergic hypersensitivity reactions to drugs, inflammatory mediators are released by nonspecific immunologic mechanisms. The drugs most frequently responsible for such reactions are nonsteroidal anti-inflammatory drugs (NSAIDs),³ with chemotherapy and biological agents increasingly involved.

In selecting diagnostic tests it is important to consider whether the reaction is immediate or nonimmediate, as summarized in Table I.

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TABLE I. Diagnostic tests of hypersensitivity reactions to drugs

Type of reaction		Type of tests
Immediate	<i>In vitro</i>	Specific IgE assays
		Flow cytometric BATs
	<i>In vivo</i>	Skin tests
Nonimmediate		Provocation tests
	<i>In vitro</i>	LTTs or LATs
		ELISPOT assays for analysis of antigen-specific, cytokine-producing cells
	<i>In vivo</i>	Delayed-reading intradermal tests
		Patch tests
		Provocation tests

IMMEDIATE (IgE-MEDIATED) REACTIONS

β -Lactams are the most important drugs involved in immediate reactions, followed by other antibacterial agents, NSAIDs, and muscle relaxants. The diagnostic approach for hypersensitivity reactions to β -lactams includes skin testing together with *in vitro* testing and, in some cases, the drug provocation test (DPT).^{4,5} This workup was updated by Torres (Malaga, Spain).

Skin prick and intradermal tests

In case of immediate reactions to penicillins, it is advisable to perform skin tests with the classic penicillin reagents penicilloyl-polylysine, the minor determinant mixture, and benzyl-penicillin,⁴⁻⁶ as well as with amoxicillin and any other suspected penicillin.^{4,5,7} With these reagents, however, the diagnostic sensitivity has been reported to be no higher than 70%,^{8,9} and the addition of other amoxicillin determinants has not improved this sensitivity.¹⁰

In case of immediate reactions to cephalosporins, it is crucial to also include the suspected compound in skin testing. In effect subjects with cephalosporin allergy may present positive responses to common penicillin determinants or respond selectively to cephalosporin determinants with a good tolerance of penicillins.¹¹⁻¹⁴ In a recent study concerning 98 patients with a well-demonstrated IgE-mediated hypersensitivity to cephalosporins,¹⁴ a reaction to a cephalosporin that shares a similar (cephalothin or cefamandole) or identical (cefaclor, cephalixin, or cefatrizine) R1 side chain with a penicillin was a significant predictor of cross-reactivity because it increased by 3-fold the risk of positive results in allergologic tests with penicillin determinants.

In subjects displaying positive results only to cephalosporins, on the basis of skin testing with a panel of different cephalosporins, 2 patterns of reactivity can be observed: one characterized by responses only to culprit cephalosporins and the other by positive responses to different cephalosporins, including the responsible ones. Cross-reactivity in the latter group (the majority of patients) could be explained by similarities in the R1 side-chain structure. For example, a cross-reactivity among ceftriaxone, cefotaxime, cefepime, cefuroxime, and ceftazidime, which have identical or similar R1 side chains, has been observed.¹¹⁻¹³ The groups at the R2 position do not seem to be as clinically important. In effect the R2 side chain and the dihydrothiazine moiety become lost in the process of conjugation of the cephalosporins to the carrier protein. Thus only the R1 side chain and part of the β -lactam ring remain bound to the carrier proteins and contribute to the chemical structure of the epitope recognition by IgE, becoming responsible for IgE-mediated hypersensitivity reactions to cephalosporins.¹⁵

However, cross-reactivity because of R2 side chains is possible. In a previously mentioned study¹² a patient with an anaphylactic reaction to cefoperazone displayed positive skin test results to both cefoperazone and cefamandole, which share an identical R2 side chain.

With regard to the sensitivity of skin testing with cephalosporins, in 3 studies concerning children,¹⁶ both children and adults,¹³ and adults¹² with histories of immediate reactions to these β -lactams, such sensitivity was 72% (31/43), 30.7% (39/127), and 69.7% (53/76), respectively. Therefore further studies should be done with a larger number of subjects to fully establish cephalosporin skin test sensitivity.

Torres highlighted that clavulanic acid is responsible for several immediate reactions to pharmaceutical preparations in which it is combined with amoxicillin^{17,18}; therefore clavulanic acid should also be tested in subjects with such reactions, especially in those displaying negative results on allergologic tests with amoxicillin.

With regard to the possibility of providing safe alternatives in subjects with penicillin allergy, Ben Said (Lyon, France) showed that cefpodoxime and ceftriaxone were tolerated by 34 patients with penicillin allergy (30 to amoxicillin, 3 to bacampicillin, and 1 to cloxacillin) who had negative results on skin testing with the cephalosporin concerned.

Other clinicians and researchers presented data concerning the usefulness of skin testing with several drugs responsible for immediate reactions, such as muscle relaxants, mAbs, platinum salts, and NSAIDs (see also below).

Garvey (Copenhagen, Denmark) highlighted the problems concerning immediate reactions during general anesthesia, in which many drugs are administered in a short time, subjects are also exposed to latex and chlorhexidine, and symptoms can mimic "normal" reactions to anesthesia induction. She presented the protocol of the Danish Anesthesia Allergy Centre, which includes allergologic tests (both *in vivo* and *in vitro*) for all drugs administered before the reaction, as well as for latex, chlorhexidine, and ethylene oxide. Skin tests should be regularly used to evaluate patients with immediate reactions during general anesthesia, as well as to reduce the risk of such reactions by identifying patients sensitized to anesthetic drugs, other compounds, or both, to be administered during the procedure and providing safe alternatives to them. In this regard the skin test concentrations for muscle relaxants used by Garvey and colleagues were those of the guidelines devised by the Société Française d'Anesthésie et de Réanimation and endorsed by the European Network for Drug Allergy.¹⁹

Castells (Boston, Mass) presented data on the usefulness of skin testing in evaluating patients with immediate reactions to mAbs, such as rituximab, infliximab, and trastuzumab, as well as to chemotherapy agents, specifically platinum salts: carboplatin, cisplatin, and oxaliplatin.^{20,21} Platinum salt reactions are uncommon during the initial courses, but the incidence increases to 27% in patients receiving more than 7 cycles. Although the positive and negative predictive values of skin testing are still unknown, more than 80% of carboplatin-reacting patients present a positive skin test result. According to Castells, skin testing with paclitaxel is not advisable because its predictive value has not been demonstrated, whereas skin testing with liposomal doxorubicin and doxorubicin is contraindicated because of high cutaneous toxicity.

Campi (Florence, Italy) reported positive results of skin tests in subjects with hypersensitivity reactions, such as injection-site and

anaphylactic reactions, to the TNF- α -blocking agents etanercept and adalimumab.²²

Finally, Barbaud (Nancy, France) found an 85.9% negative predictive value of skin tests with different drugs by performing provocation tests in 85 subjects with histories of immediate reactions and negative results in skin testing: 12 (14.1%) of them reacted.²³

***In vitro* tests**

Serum specific IgE assays are still the most common *in vitro* methods for evaluating immediate reactions. The most validated immunoassay, ImmunoCAP (Phadia, Uppsala, Sweden), has been widely used for evaluating immediate reactions to β -lactams, mainly penicillins, with a specificity approaching 90% and a sensitivity of up to 50%.^{24,25} However, Perez-Inestrosa (Malaga, Spain) reported on the production by nanotechnology of well-designed conjugates of β -lactams with macromolecules, which might improve the sensitivity of serum specific IgE assays.

Studies comparing skin tests and specific IgE assays indicate that the 2 methods are not totally equivalent. In this connection, Campi, using experimental prototypes of ImmunoCAP assays, did not find specific IgE to etanercept and adalimumab in the sera of subjects with hypersensitivity reactions and immediate-reading skin tests to these TNF- α antagonists. On the contrary, Pagani (Asola, Italy) used an experimental prototype of ImmunoCAP for carboplatin, which confirmed skin-test result positivity in 2 patients and was positive in 1 patient who had negative skin prick test responses and did not undergo intradermal tests.

The diagnostic role of the flow cytometric basophil activation test (BAT) was updated by Ebo (Antwerp, Belgium) and Strum (Graz, Austria), who emphasized the increasing importance of this test, particularly in evaluating immediate reactions to β -lactams, muscle relaxants, and other drugs for which no alternative *in vitro* tests are available.^{26,27} The BAT detects specific markers that are expressed on the surfaces of blood basophils after their activation by incubation with the responsible drug. At present, the most commonly used markers in BATs are CD63 and CD203c. In particular, Sturm analyzed literature data and showed that the BAT sensitivity and specificity concerning muscle relaxants varied from 36% to 92% and 93% to 100%, respectively, whereas sensitivity and specificity regarding β -lactams varied from 33% to 67% and 79% to 100%, respectively. Ebo performed the BAT in 100 subjects with hypersensitivity reactions to rocuronium; BAT sensitivity was about 78%, and specificity was 100%. However, additional comprehensive studies in large samples are required to further validate the technique and provide a definitive assessment of its sensitivity.

All experts agreed that the BAT is not advisable in subjects with histories of hypersensitivity reactions to NSAIDs, especially those who reacted to several compounds (multiple reactors).

DPTs

DPTs or graded challenges remain the gold standard for the identification of an eliciting drug when allergologic test results are negative, not available, or not validated.^{4-6,28} In particular, the sensitivity of allergologic tests is not 100%, and therefore in selected cases DPTs are necessary. They not only allow drug hypersensitivity to be diagnosed but also allow it be excluded in a large percentage of reactions experienced by patients with negative

skin test results, *in vitro* test results, or both. In the Danish Anesthesia Allergy Centre protocol DPTs are extensively used; nevertheless, some suspected drugs are only tested by administering up to maximum of one tenth of the therapeutic dose, and muscle relaxants are not tested. This approach allows the diagnosis of hypersensitivity to dextrans, which is based on an IgG-mediated mechanism, to be made and reduces the risk of both false-positive test results (eg, to low-molecular-weight heparins) and false-negative test results (eg, to opioids).

In the diagnosis of nonallergic hypersensitivity reactions to NSAIDs, provocation tests with the suspected drug still represent the gold standard.

Bousquet (Montpellier, France) showed data from a multicenter study (France, Italy, and Portugal)²⁹ that assessed the negative predictive value of DPTs with β -lactams. In this study 457 patients who had either immediate or nonimmediate reactions to β -lactams were contacted at least 6 months after a negative allergologic workup, including DPTs. Only 118 (32.3%) of the 365 who responded took the suspected β -lactam found to be negative in the allergologic workup. Nine of the 118 subjects reacted, and therefore the negative predictive value of DPTs with β -lactams was 94.1%. In another study of the same group, the negative predictive value of DPTs with NSAIDs was 93%: 8 of the 128 patients who took the previously tolerated compound reacted.

NONIMMEDIATE (T CELL-MEDIATED) REACTIONS

The skin is the organ most frequently affected in these reactions, with a spectrum of clinical pictures ranging from mild reactions, such as maculopapular rash and delayed-appearing urticarial exanthema, to severe reactions, such as AGEF, Stevens-Johnson syndrome (SJS), and TEN.^{30,31} Patch tests, together with delayed-reading intradermal tests, *in vitro* tests, and DPTs, are useful tools for evaluating nonimmediate drug reactions.^{6,30}

Skin testing

Barbaud emphasized that patch tests can be performed with any form of commercial drug and are safer than intradermal tests. For this reason, if it is necessary to evaluate patients with severe skin reactions (eg, TEN, severe bullous exanthems, and AGEF), patch tests should be used as the first line of investigation; in case of positive results, intradermal testing can be avoided.³²

Haddad (Créteil, France) presented the results of a retrospective study that evaluated 111 patients with severe cutaneous adverse reactions to drugs, such as pristinamycin, amoxicillin, sulfamethoxazole, carbamazepine, and NSAIDs. The rate of positive responses to patch tests in patients with AGEF, DRESS, SJS/TEN, and fixed drug eruption was 63% (20/32), 50% (14/28), 26% (10/39), and 17% (2/12), respectively. The proportion of positive patch test results was significantly ($P = .003$) higher in patients with nonbullous reactions (AGEF + DRESS) than in those with bullous reactions (SJS/TEN + fixed drug eruptions). In this study no severe side effects were reported.

However, patch tests are less sensitive than intradermal tests, and their sensitivity can vary depending on the vehicle used and the drug tested. In this connection, Campi reported positive results of delayed-reading intradermal tests in subjects with injection-site reactions to the TNF- α -blocking agents etanercept and

TABLE II. Classification of hypersensitivity reactions to aspirin and NSAIDs

Reaction time	Clinical manifestation	Type of reaction	Underlying disease	Putative mechanism
Acute (immediate to several hours)	Rhinitis/asthma (AERD)	Cross-reactive (ie, induced by multiple NSAIDs)	Asthma/rhinosinusitis/nasal polyps	Inhibition of COX-1
	Urticaria/angioedema (aspirin-exacerbated cutaneous disease)	Cross-reactive	Chronic idiopathic urticaria	Inhibition of COX-1 Unknown (autoreactivity?)
	Urticaria/angioedema/anaphylaxis	Cross-reactive	None	Inhibition of COX-1 Unknown (autoreactivity?)
	Urticaria/angioedema/anaphylaxis	Selective (ie, induced by a single NSAID)	Atopy/food allergy/drug allergy	Specific IgE
Delayed (>24 h)	Fixed drug eruption	Selective or cross-reactive	Usually none	T cells
	Severe bullous reaction			Cytotoxic T cells
	Maculopapular eruption			Natural killer cells
	Contact and photocontact dermatitis			Other
	Pneumonitis			
	Aseptic meningitis			
	Nephritis			

adalimumab.²² All these subjects had negative results on patch tests with the responsible drugs.

Barbaud also assessed the negative predictive value of skin tests (delayed-reading intradermal tests, patch tests, or both) in 175 subjects with nonimmediate reactions to numerous drugs, including β -lactams. Only 15 (8.6%) of the subjects with negative results on skin tests reacted to DPTs with the suspected drugs (negative predictive value, 91.4%).²³

In vitro tests

A cellular response involving drug-related T-cell activity may be assessed *in vitro* by means of both the lymphocyte transformation test (LTT) and the flow cytometric lymphocyte activation test (LAT).^{33,34} In the latter test the activation is measured based on up-regulation of the activation marker CD69. The results of both tests were shown by Pichler's group (Bern, Switzerland), which evaluated 97 patients. The sensitivity and specificity of the LAT were 16.7% and 97.8% and those of the LTT were 11.6% and 96.8%, respectively. Therefore the sensitivity of both tests was lower than that previously found by the same group.^{33,34} However, as previously reported by Lochmatter et al³⁵ and highlighted by Martin (Bonn, Germany), the combination of these tests with the assay of drug-specific cytokines (eg, IF- γ , IL-2, IL-5, IL-8, and IL-12) can increase the sensitivity and specificity to 48% and 82%, respectively, in the study of Pichler's group presented at the DHM4.

Nicolas' group (Lyon, France) presented data demonstrating that the enzyme-linked immunospot (ELISPOT) assays for the analysis of the frequency of antigen-specific, cytokine-producing cells is a useful tool for evaluating maculopapular rashes associated with amoxicillin,³⁶ as well as DRESS provoked by different drugs. Specifically, Ben Said et al performed ELISPOT assays for the detection of IFN- γ , IL-5, IL-17, and granzyme B after stimulation of PBMCs with the drugs responsible for DRESS. Results of ELISPOT assays were positive in 10 of 11 subjects with positive patch test results and negative in 6 subjects with negative skin test results. Therefore there was a correlation between the detection of specific T cells by using *in vivo* patch tests and *ex vivo* ELISPOT assays.

Whitaker (Leeds, United Kingdom) emphasized the usefulness of the LTT in nonimmediate reactions to β -lactams, specifically to piperacillin, in subjects with cystic fibrosis. In effect, 21 (72.4%) of 29 patients with hypersensitivity reactions to piperacillin had positive responses on the LTT, whereas only 4 (13.8%) had positive responses on delayed-reading intradermal tests.

Gomez (Malaga, Spain) showed that the use of dendritic cells in the LTT improved its sensitivity in evaluating patients with nonimmediate reactions to β -lactams,³⁷ heparins,³⁸ and glucocorticoids.³⁹

Abe (Hokkaido, Japan) presented data concerning the usefulness of a rapid (<15 minutes) immunochromatographic test for the detection of high levels of serum granulysin in an early stage of SJS/TEN. Granulysin is the most highly cytotoxic molecule expressed in blister cells.⁴⁰ Results of this assay were positive in 4 of 5 patients with SJS/TEN, whereas only 1 of 24 patients with ordinary types of drug-induced skin reactions had positive bands (sensitivity, 80%; specificity, 95.8%).

DPTs

In nonimmediate reactions to drugs, DPTs are advisable in cases of mild reactions, such as maculopapular exanthems and delayed-appearing urticaria, with negative results in allergologic workup.²⁸ In effect, negative results on DPTs allow a drug hypersensitivity to be ruled out (see also DPTs in immediate reactions).

DIAGNOSIS OF HYPERSENSITIVITY REACTIONS TO NSAIDS

A great deal of importance was given to this topic. Specifically, a roundtable was organized to establish a consensus on some controversial issues regarding the diagnosis of hypersensitivity reactions to NSAIDs. Kowalski (Lodz, Poland) acted as chairman, and the other participants were Asero (Paderno Dugnano, Italy), Blanca (Malaga, Spain), Sanchez-Borges (Caracas, Venezuela), and Woessner (San Diego, Calif). Participants agreed with the classification proposed by Kowalski, which distinguished between acute (appearing from a few minutes to several hours after the last NSAID administration) and delayed

(appearing after >24 hours) reactions (Table II). As previously done,^{41,42} acute reactions were further classified into one of 4 categories: (1) NSAID-induced rhinitis and asthma in patients with underlying asthma, nasal polyps, and rhinosinusitis (ie, aspirin-exacerbated respiratory disease [AERD]); (2) NSAID-induced urticaria and angioedema in patients with underlying chronic idiopathic urticaria (ie, aspirin-exacerbated cutaneous disease); (3) multiple drug-induced urticaria/angioedema/anaphylaxis; and (4) single drug-induced urticaria/angioedema/anaphylaxis. The main putative pathogenic mechanisms are shown in Table II: (1) inhibition of the constitutive isoform of COX-1 (categories 1-3); (2) specific IgE (category 4); and (3) T cells (delayed reactions). However, Asero believed that a mechanism based uniquely on COX-inhibition was unlikely in subjects with multiple drug-induced cutaneous reactions who do not also tolerate selective COX-2 inhibitors. In effect, he demonstrated an autoreactivity (ie, circulating histamine-releasing factors) in such subjects on the basis of positive responses on autologous serum skin tests.⁴³ During the discussion, a pathogenic role of the sensitization to foods was also hypothesized. In effect, NSAIDs can increase intestinal absorption of food allergens and contribute to elicit hypersensitivity reactions to them.⁴⁴ In these cases neither NSAID intake nor food ingestion alone elicits reactions. Some participants (Asero, Blanca, and Sanchez-Borges) believed that the ingestion of food containing lipid transfer proteins could play an important role in provoking these reactions.

According to Blanca, subjects can be classified as “cross-reactors” (categories 1, 2, and 3) when they have experienced 2 or more reactions to at least 2 different drugs that include strong COX-1 inhibitors or have experienced 1 or more reactions to drugs belonging to a single chemical group and display a positive DPT response to an alternative strong COX-1 inhibitor.

With regard to the first category, the diagnosis of AERD is usually established on the basis of the clinical picture of chronic rhinosinusitis and moderate-to-severe asthma with NSAID-induced exacerbations. However, when a definitive diagnosis is required, a controlled oral challenge with aspirin can be performed. Woessner considered the oral aspirin challenge to be the gold standard in the diagnosis of AERD and described the protocol followed in the Scripps Clinic. She distinguished 4 different types of positive responses to aspirin challenges: (1) classic (ie, a decrease of $\geq 20\%$ in FEV₁ plus naso-ocular symptoms); (2) pure lower (ie, a decrease of $\geq 20\%$ in FEV₁); (3) partial asthma (ie, a decrease in FEV₁ between 15% and 20% with a naso-ocular reaction); and (4) laryngospasm. A response was considered negative if subjects tolerated 650 mg of aspirin.

The diagnosis of aspirin-exacerbated cutaneous disease is based on history. Most participants agreed that these patients should not undergo challenges with the suspected drugs and that they should be considered cross-reactors (or multiple reactors), even though they have histories of urticaria induced by a single NSAID.

As far as the third category is concerned, Asero reported the results of a study specifically designed to detect its prevalence.⁴⁵ Among 261 subjects with NSAID-induced urticaria, 94 (36%) were classified as belonging to category 3 on the basis of history and response to challenges. As in categories 1 and 2, the diagnosis is based on history; subjects should not be challenged with suspected drugs unless concomitant etiologic factors, such as food allergen ingestion, are suspected.

Cross-reactive patients (or multiple reactors) have to avoid the culprit drugs, as well as others with a similar or higher capability

of inhibition of COX-1. Therapeutic options can be found in drugs such as weak COX-1 inhibitors (acetaminophen), preferential (nimesulide, meloxicam), or both, or highly selective COX-2 inhibitors (coxibs).⁴² In any case controlled challenges with alternative NSAIDs are advisable before prescribing them.

With regard to category 4, subjects can be classified as “selective responders” if they have experienced 1 or more reactions to a single drug with good tolerance of strong COX-1 inhibitors belonging to other groups or even to the same group with a slightly different chemical structure. According to all participants, if subjects experienced 1 or more reactions to the same drug and it is not known whether they will tolerate a strong COX-1 inhibitor, they should undergo a challenge with a strong COX-1 inhibitor (eg, aspirin in subjects who reacted to ketoprofen and *vice versa*).

Blanca pointed out that the selective responders evaluated by the Spanish Network for the Study of Adverse Reactions to Drugs and Allergens often had experienced anaphylactic reactions. In these patients, moreover, the time interval between drug intake and development of symptoms usually was shorter and the eliciting dose lower than in cross-reactors.

All participants agreed about the usefulness of evaluating these patients to detect an IgE-mediated pathogenic mechanism on the basis of positive responses on skin tests, *in vitro* tests (serum specific IgE assays and BATs), or both. Pyrazolones, diclofenac, and propionic acid derivatives are the drugs most frequently responsible for IgE-mediated reactions.⁴⁶ With regard to diclofenac, Kynaciyan and colleagues (Vienna, Austria), using a murine model, demonstrated that gastric acid suppression can be a causative mechanism in the induction of diclofenac IgE-mediated hypersensitivity. In their study,⁴⁷ only mice receiving albumin-coupled diclofenac under gastric acid suppression had anti-diclofenac IgG1 and IgE in a dose-dependent manner, whereas no immune responses were induced by diclofenac alone or without acid gastric suppression. The aforementioned antibodies triggered mast cell degranulation and were responsible for positive skin test results. Moreover, they proved that testing with diclofenac coupled to keyhole limpet hemocyanin (KLH), which is a multivalent antigen, improved the sensitivity of both *in vivo* and *in vitro* tests. They performed skin tests and specific IgE assays in 2 subjects with urticarial reactions to diclofenac and in 2 healthy control subjects using diclofenac, diclofenac-KLH, and KLH. In both tests the 2 patients had positive responses only to diclofenac-KLH.

Delayed reactions include several clinical pictures, which range from mild exanthems to severe reactions, such as SJS, TEN, and DRESS.^{48,49} In some delayed reactions to NSAIDs, such as diclofenac, piroxicam, acetaminophen, and pyrazolones, a T cell-mediated hypersensitivity mechanism may be involved, and patch testing, together with delayed-reading intradermal tests and *in vitro* tests, can be useful in assessing such reactions.³⁰

DESENSITIZATION

Desensitization is a procedure to induce a temporary tolerance of drugs responsible for hypersensitivity reactions. The definition “induction of drug tolerance” has also been proposed as a more appropriate expression to encompass not only IgE-mediated desensitization procedures but also other non-IgE-mediated desensitizations.⁶ In the DHM4 particular attention was dedicated to this topic.

Concerning desensitization to aspirin in patients with AERD, Woessner presented a protocol in which more than 1,000 subjects were desensitized in the Scripps Clinic. Subjects selected for aspirin desensitization were (1) all patients with AERD, except those whose symptoms were controlled with topical steroids, long-acting β -agonists, and leukotriene-modifying drugs alone; (2) patients with recurrent or chronic sinusitis and nasal polyps; and (3) patients who required antiplatelet therapy with aspirin or other COX-1-inhibiting drugs.

Subjects successfully desensitized tolerate 650 mg of aspirin. They present a rapid improvement in nasal congestion and can tolerate other strong COX-1 inhibitors, such as ibuprofen and naproxen (cross-desensitization). However, bronchial hyperreactivity does not change in these subjects; in fact, methacholine challenge results continue to be positive. Nevertheless, after desensitization, a decrease in sinus infections, olfactory scores, and nasal and asthma symptoms, with a reduction in the numbers of visits and hospitalizations per year, as well as the average dose of prednisone, has been demonstrated.⁵⁰ With regard to maintenance, aspirin is typically given at 650 mg twice daily, but many patients can continue maintenance therapy at 325 mg twice daily. In subjects who only need cardiovascular disease prophylaxis, the tolerance state can be maintained with 81 mg.⁵¹

Castells presented data concerning a standardized 12-step, 6-hour protocol developed at the Brigham and Women's Hospital for achieving temporary tolerance of chemotherapeutic agents and mAbs.^{20,21} With regard to the former, 98 patients who had experienced hypersensitivity reactions to platinum salts (carboplatin, oxaliplatin, and cisplatin), paclitaxel, liposomal doxorubicin, doxorubicin, or rituximab were administered intravenously or intraperitoneally. Of the 413 desensitizations performed, 111 (26.9%) elicited mild reactions, and 24 (5.8%) elicited severe reactions. No life-threatening reactions or deaths occurred during the procedure, and all patients received their full target dose.²⁰ Castells and colleagues also performed 105 rapid desensitizations in 23 patients with hypersensitivity to mAbs, including rituximab, infliximab, and trastuzumab. All but 1 of the desensitizations were successfully completed. They observed 30 (28.6%) hypersensitivity reactions: 27 mild, 1 moderate, and 2 severe.²¹ Therefore this protocol proved to be safe and effective.

CONCLUSIONS AND FUTURE DIRECTIONS

In diagnosis the patient's history is fundamental; the allergologic examination includes *in vivo* and *in vitro* tests selected on the basis of the clinical features.

Prick, patch, and intradermal tests are the most readily available forms of allergy testing. Serum specific IgE assays are still the most common *in vitro* methods for diagnosing immediate reactions; however, they are available only for a few drugs.

The sensitivity of allergologic tests is not 100%, and therefore in selected cases DPTs are necessary. These remain the gold standard for the identification of an eliciting drug when allergologic test results are negative, not available, or not validated, as in most hypersensitivity reactions to NSAIDs. However, new diagnostic tools, such as the BAT, the LAT, and ELISPOT assays for analysis of the frequency of antigen-specific, cytokine-producing cells, have been developed. Their routine use could increase the sensitivity of diagnostic workups, thus reducing the need for DPTs. The sensitivity of both *in vivo* and *in vitro* tests could also

be increased by coupling the suspected drugs with carrier molecules, as in the case of diclofenac-KLH.⁴⁷ Moreover, when hypersensitivity reactions are not caused by the parent compound but by its metabolites, the identification and use of the latter in diagnostic tests could be crucial for improving the sensitivity of these tests, as recently demonstrated by Castrejón et al,⁵² by performing lymphocyte proliferation studies in subjects with hypersensitivity reactions to sulfonamides.

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